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A CASE OF

CONGENITAL PULMONARY STENOSIS, WITH SPECIAL CONSIDERATION OF THE NATURE OF THE SECONDARY BLOOD CHANGES

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CONGENITAL PULMONARY STENOSIS, WITH SPECIAL CONSIDERATION OF THE NATURE OF THE SECONDARY BLOOD CHANGES.[1]

In a previous paper one of us (F. P. W.)[2] described the case of a young man, aged 22 years, with congenital heart disease, great cyanosis, and extreme secondary polycythæmia (polyglobuly)—namely, over 10,000,000 red cells to the cubic millimetre of blood. Evidence was furnished in support of the modern doctrine that the excess in the number of red blood corpuscles in such cases was largely of a compensatory (conservative) nature; that it was a manifestation of the attempt on the part of the bone-marrow to make up for imperfect oxygenation of the blood and tissues of the body by a numerical increase of the red cells—that is to say, of the oxygen carriers of the blood; that it represented, in fact, a vital compensatory reaction analogous to the increase of the polymorphonuclear leucocytes in the blood, consequent on streptococcal invasions, &c. It was furthermore pointed out that the figures obtained by actual blood-counts might make one under-estimate rather than over-estimate the total numerical excess of erythrocytes in the body, for there was considerable evidence indicating that when, in chronic cardiac cases, the erythrocyte-count per cubic millimetre of blood was above the normal (relative polycythæmia) the total volume of blood in the whole body was likewise

[1] A paper read before the Clinical Section of the Royal Society of Medicine on Jan. 13th, 1911.

[2] F. P. Weber: Edinburgh Medical Journal, 1909, New Series, vol. ii., p. 18.

excessive, a supposition confirmed by the congested appearance of the ears, lips, nose, tongue, and retinæ in many cases

In the present case we have been able to obtain additional evidence (pointing to the same conclusions) by means of the estimation of the total hæmoglobin and total blood volume in the body by Haldane and Lorrain Smith's carbon monoxide method. As concentration of the blood resulting from delayed circulation (stasis) in the capillaries might partly account for the polycythæmia in chronic cardiac cases, we have in the present case attempted to measure (as was proposed in the paper already referred to) the degree of any such blood concentration (if present) by estimating the total solid residue in the patient's blood serum, just as Weintraud and Senator estimated it in cases of so-called "splenomegalic polycythæmia" or "erythræmia."[3]

It has been suggested by Bence, von Koranyi, Mohr, Lommel,[4] and others, and quite recently again by E. C. Seufert,[5] that the excess of red blood corpuscles in cases of splenomegalic polycythæmia (erythræmia) may be accounted for as a compensatory vital reaction on the supposition that the hæmoglobin is defective in quality in such a way as to lower its capacity for taking up oxygen. Similarly it might be suggested that a lowered oxygen capacity of the hæmoglobin is the real cause of polycythæmia, when this is met with in cases of congenital (and acquired) heart disease. There is, however, no evidence that the oxygen capacity of the hæmoglobin is abnormally low or abnormally high in either group of cases, unless Mohr's observation be correct that it was actually diminished in a case of congenital pulmonary stenosis with secondary polycythæmia, which was specially examined in this respect. In cases of polycythæmia with splenomegaly the oxygen capacity of the hæmoglobin has

[3] Vide F. P. Weber: Polycythæmia, Erythrocytosis, and Erythræmia, Quarterly Journal of Medicine, Oxford, 1908, vol. ii., pp. 85–134. By analogy with the terms "leucocytosis" and "leukæmia" the term "erythrocytosis" is sometimes employed to signify a secondary ("reactive") increase of the red blood corpuscles so as to distinguish it from a condition ("erythræmia") in which the increase of the red cells is apparently due to a primary disorder of the erythrocyte-producing tissue of the body.

[4] These authors are quoted by F. P. Weber, Quarterly Journal of Medicine, loc. cit., p. 113.

[5] E. C. Seufert: American Journal of the Medical Sciences, Philadelphia, 1910, vol. cxl., p. 827. Seufert assumes, as causa causans of erythræmia, some deterioration in the quality of the hæmoglobin.

never been found notably reduced. Thus, in two cases of Lommel and one of Mohr it was found to be at the lowest level within normal limits; nor did cases referred to by Senator (1906) and Parkes Weber (two cases in which A. E. Boycott examined the oxygen capacity of the blood) furnish any support to Bence's suggestion.[6] Of great importance are the observations of P. Morawitz and W. Röhmer[7] on the subject They apparently find that the oxygen capacity of the hæmoglobin does not differ in health or disease from the ordinary standard, even if in some conditions (affecting the salts in the blood) the oxygen is much more readily dissociated from the hæmoglobin than in others. Moreover, we may add that in the rare cases of chronic methæmoglobinæmia and chronic sulph-hæmoglobinæmia (in which less oxygen than normally can be taken up by the red corpuscles) secondary polycythæmia has not been noted.

The patient in the present case is an intelligent young man of Jewish parentage, aged 29 years, a French polisher by trade, who first came under observation on account of temporary bronchitic symptoms. In spite of his congenital heart disease (see later) and the lividity, polycythæmia, &c., connected with it, he has usually enjoyed good health. He has great cyanosis of the lips, tongue, ears, nose, fingers, and toes; the cyanosis varies in degree from time to time and is increased by muscular exercise; it does not seem to be markedly lessened by oxygen inhalation. There is a tendency to epistaxis and there is decided "clubbing" of the fingers and toes. A skiagram of the hands shows the absence of any osteo-arthropathy; the phalangeal bones appear normal. By percussion and Roentgen ray examination the heart is found to be slightly enlarged to the right, the cardiac dulness reaching one finger-breadth to the right of the sternum. There is a rather loud systolic murmur, best heard over the second and third left intercostal spaces, close to the left border of the sternum, doubtless due to pulmonary stenosis. From what has been found in similar cases, it is highly probable that in addition to the pulmonary stenosis there is a considerable defect in the interventricular septum, but of this we have no certain physical signs. Beyond these

[6] Cases quoted by F. P. Weber, Quarterly Journal of Medicine loc. cit., p. 114.

[7] P. Morawitz and W. Röhmer: Ueber die Sauerstoffversorgung bei Anämien, Deutsches Archiv für Klinische Medicin, 1908, vol. xciv., pp. 529, et seq.

points there is nothing special to be noted in regard to the examination of the thorax and abdomen. The liver and spleen cannot be felt and are apparently not enlarged. Brachial systolic blood pressure, about 100 mm. Hg. Examination of the urine shows nothing abnormal except that there is intermittent albuminuria of the orthostatic type. The urine passed immediately on getting out of bed in the morning is free from albumin, whereas that passed later yields a more or less thick cloud of albumin; but when microscopically examined it was free from tube-casts. There is no sexual or other form of infantilism. As in cases of "splenomegalic polycythæmia" ("erythræmia") the conjunctivæ tend to be suffused owing to vascular engorgement, and by ophthalmoscopic examination the retinal veins are seen to be distended. In January, 1910, a retinal hæmorrhage at the lower part of the left optic disc was noted.

Blood examination.—Red cells (capillary blood), 10,110 000 per cubic millimetre of blood; white cells, 10,275 per cubic millimetre; hæmoglobin, 200 per cent. by Sahli's method, 180 per cent. (on a later occasion) by Haldane's method. The blood is so "thick" that it is relatively difficult to suck it up into a capillary tube; when the fresh blood has been centrifugalised in a cylindrical tube about nine-tenths instead of the normal one-half of the column are taken up by the corpuscular layer. A differential count of 500 white corpuscles (made in September, 1910) gave polymorphonuclear leucocytes 73 per cent., small lymphocytes 19·8 per cent., large lymphocytes 5·2 per cent., transitionals 1·0 per cent., eosinophiles 0·6 per cent., mast-cells 0·4 per cent.; the red corpuscles in the blood-film showed nothing abnormal excepting that three nucleated red corpuscles (normoblasts) were seen during the count of 500 white cells.

The viscosity of the blood as estimated (at 20° C) by Determann's clinical viscosimeter,[8] was found to be 35·9 times that of water (at 20° C.), that is to say, very greatly in excess of the normal. The coagulability of the blood was less than that of normal blood; the coagulation time, as

[8] Determann: Verhandlungen des Kongresses für Innere Medicin, Wiesbaden, 1907, vol. xxiv., p. 533. E. Münzer and F. Bloch, in their work, Experimentelle Beiträge zur Kritik der Viskositätsbestimmungsmethoden (Zeitschrift für Experimentelle Pathologie und Therapie, Berlin, 1910, vol. vii., pp. 174–184), find that Determann's clinical viscosimeter gives too high values. Anyhow, in our present case, the viscosity is, beyond all doubt, excessive.

measured by Sir A. E. Wright's coagulometer, being 15 minutes.[9] The resistance of the blood towards hæmolysis, as tested by the addition of the washed red corpuscles to graduated hypotonic salt solutions, appeared to be rather below the normal standard; very slight hæmolysis was observed when the washed red cells were added to a 0·72 per cent. aqueous solution of sodium chloride, and was complete with a solution of 0·54 per cent.

Specific gravity of the blood (pyknometer method), 1·086; specific gravity of the blood serum (pyknometer method), 1·036; dry residue of the blood, 29·4 per cent.; dry residue of the blood serum (only half a gramme of serum was obtained, which, owing to slight hæmolysis, was coloured red with hæmoglobin), 10·38 per cent.

On Sept. 10th, 1910, Dr J. S. Haldane and Dr. C. Gordon Douglas kindly estimated the patient's total oxygen capacity (or rather the oxygen capacity of the total hæmoglobin of his blood) and his total blood volume by Haldane and Lorrain Smith's carbon monoxide method.[10] For their investigation and the following report (by Dr. Douglas) we take this opportunity of thanking them. Precautions were taken to guard against a possible source of fallacy (in the method in question) which may arise if insufficient time is allowed for the even distribution of the carbon monoxide through the blood before taking the samples of blood for analysis. The carbon monoxide was given at a slow rate (30½ minutes were occupied by this) by means of the original apparatus employed by Haldane and Lorrain Smith, and the patient was required to breathe for another four minutes into this apparatus. Then he breathed for 17 minutes into a closed respiration apparatus with an effective volume of 15 litres containing pure air, the oxygen in this being kept constant automatically by means of an arrangement similar to that devised by Regnault and Reiset. The amount of carbon monoxide lost

[9] In cases of erythræmia (splenomegalic polycythæmia) and polycythæmia secondary to cardio-pulmonary affections Parkes Weber has observed that the coagulation of the blood seems to be delayed, as if diminution of coagulability were compensatory (in the modern teleological sense) to great increase of blood-viscosity in these cases (the increased tendency to thrombosis, connected with the excessive blood-viscosity and delayed capillary circulation being to some extent neutralised by the diminution of blood-coagulability).

[10] Haldane and Lorrain Smith: Journal of Physiology, 1900, vol. xxv. p. 331.

by the patient into this closed space was sufficiently small to be neglected. During the experiment 239 c.c. of carbon monoxide (measured at 0° C. and 760 mm. Hg pressure) were administered to the patient. Two samples of blood were taken from the finger, one 11½ minutes before the end of the experiment and the other at the end of the experiment. The degree to which the blood was saturated with carbon monoxide—namely, 11·9 per cent.—was the same in the two samples, and there can therefore be little doubt that the time allowed was long enough for the gas to become evenly distributed through the blood. The total carbon monoxide (or oxygen) capacity of the subject (or rather of the hæmoglobin in his blood) was therefore 239/11·9 × 100 = 2010 c.c. Since the percentage of hæmoglobin by Haldane's hæmoglobinometer was 180, corresponding to an oxygen (or carbon monoxide) capacity of 33 3 per cent., the volume of the patient's blood was 2010/33·3 × 100 = 6040 c.c. The patient's weight without clothes was 7 st. 4 lb., or 46 kilos, and he had therefore 4·37 c.c. of oxygen capacity (in his hæmoglobin) and 13·13 c.c. of blood per 100 grammes of body weight. Haldane and Lorrain Smith's original results for a series of 14 normal men were 0·98 c.c of oxygen capacity and 4 78 c.c. of blood per 100 grammes of body weight; Plesch [11] gives 1·12 c c. of oxygen capacity and 4·78 c c. of blood, and Oerum [12] gives 5·2 c.c. of blood. It is doubtful (Dr. Douglas writes us) whether the fallacy alluded to above was excluded in all these cases, since more recent observations [13] have shown in three perfectly normal persons an oxygen capacity of about 1·4 c c. and a blood volume of about 7·5 c.c. per 100 grammes of body weight. In the present case, however, there can be no doubt that both the oxygen capacity and the blood volume per 100 grammes of body weight are very much greater (especially, of course, the former) than those in normal persons, though, on account of the difficulty just mentioned, the values cannot at present be definitely expressed as multiples of normal values.

[11] Plesch: Zeitschrift für Experimentelle Pathologie und Therapie, 1909, vol. vi., p. 380.

[12] Oerum: Deutsches Archiv für Klinische Medicin, 1908, vol. xciii., p. 356.

[13] See Boycott and Douglas, Guy's Hospital Reports, 1908, vol. lxii., p. 157; and C. G. Douglas, Journal of Physiology, 1910, vol. xl., p. 471.

In regard to these remarks of Dr. Douglas, it may be noted that according to the old idea that the total blood in the whole human body averages about one-thirteenth of the body weight (or 7·7 grammes blood per 100 grammes body weight), the normal weight of the blood in a person of the present patient's body weight (46 kilogrammes) should be about 3538½ grammes.

The present case may be regarded as an extreme example of cyanosis and polycythæmia[14] in an adult secondary to congenital heart disease. It shows that in these cases, as in "splenomegalic polycythæmia" ("erythræmia"), not only the number of red corpuscles and the amount of hæmoglobin per cubic millimetre of blood are greatly above the normal, but so also are the amount of hæmoglobin (as measured by the oxygen capacity) and the volume of blood per 100 grammes of body weight; there is, in fact, a condition of true plethora ("polyhæmia") present, so that the degree of absolute polycythæmia is much greater even than the degree of relative polycythæmia.

The polycythæmia in these cases can therefore only to a very limited extent, if at all, be accounted for by inspissation of the blood owing to blood stasis in the capillaries. But it must, as in "splenomegalic polycythæmia" ("erythræmia"), be almost entirely due to an increased formation of red blood cells in the bone marrow. In the present case the great hæmopoietic activity of the bone marrow is confirmed by the rather large percentage (though it is within normal limits) of the polymorphonuclear leucocytes (73 per cent. of the white cells) and by the presence of a few nucleated red cells in the circulating blood.

That polycythæmia in chronic cardiac cases is not merely "relative polycythæmia"—that, in fact, it is not merely

[14] F. Parkes Weber in the Edinburgh Medical Journal (1909, New Series, vol. ii., p. 18) gave references to 14 cases of congenital pulmonary stenosis, or more complicated forms of congenital heart disease, in which blood counts showed that there were over 8,000,000 red cells in the cubic millimetre of blood. In the case he himself described, a man aged 22 years, the red cells were 10,300,000 in the cubic millimetre. In cases of congenital heart disease published since then counts of over 9,000,000 red cells have been recorded by C. A. Fife (Proceedings Philadelphia Pediatric Society, Dec. 14th, 1909; British Journal of Children's Diseases, London, 1910, vol. vii., p. 24), by T. R. Whipham (Proceedings Royal Society of Medicine, 1910, vol. iii., Section for the Study of Disease in Children, p. 149, and Ibid., 1911, vol. iv., p. 3), and by W. Bie and W. Maar (Deutsches Archiv für Klinische Medicin, 1910, vol. xcix., p. 382.)

due to concentration of the blood owing to delayed circulation (blood stasis) in the capillaries—has been to some extent shown by the numerical increase of the red cells being found not only in the blood from capillaries and veins, but likewise in that from the arteries. Thus, G. A. Gibson [15] on one occasion, in a boy, aged 16 years, supposed to be suffering from mediastinal pericarditis, found the erythrocytes in the arterial blood to be 7,000,000; in the capillary blood, 8,500,000; and in the blood from a vein, 10,000,000. Palleri and Mergari,[16] in a case of congenital pulmonary stenosis, counted the red cells in capillary blood from the finger at 6,650,000; in venous blood from a vein in the arm at 6,400,000; and in arterial blood from the temporal artery at 5,950,000.

The dry residue of the blood (29·4 per cent.) and of the blood serum (10·38 per cent.) in our present case may be compared with the following data given by W. Bie and W. Maar [17] in their account of a case (a man aged 19 years) of cyanosis and polycythæmia (6,500,000 to over 10,000,000 red cells in the cubic millimetre of blood) secondary to congenital heart disease:—

Dry residue of blood (from a vein)	25·41 to 25·45 per cent.
Dry residue of blood serum	8·87 to 8·88 ,,

As approximate values for normal persons the following figures may be given [18]:—

Dry residue of blood	20·3 to 22·8 per cent.
Dry residue of blood serum... ...	9·21 to 10·50 ,,
Albumin in blood	22·6 per cent. (von Jaksch).
Albumin in blood serum	8·8 ,, ,,
Specific gravity of blood	about 1·060
Specific gravity of blood serum...	1·028 to 1·031.

The excess of red corpuscles accounts, of course, for the rather large percentage of dry residue and the rather high specific gravity in polycythæmic blood as a whole, but it is

[15] G. A. Gibson: The Lancet, Jan. 5th, 1895, p. 24.

[16] Palleri and Mergari, quoted by Guiserne, Des Polyglobulies, Thèse de Paris, 1902.

[17] W. Bie and W. Maar: Deutsches Archiv für Klinische Medicin, Leipzig, 1910, vol. xcix., p. 382.

[18] Compare also the figures quoted in H. Vierordt's Anatomische, Physiologische und Physikalische Daten und Tabellen, third edition, Jena, 1906, pp. 191–203.

with the corresponding figures for the blood serum that we are specially concerned. The fact that these latter are not much, or not at all, above normal limits shows that the blood plasma in polycythæmia secondary to congenital heart disease (as also in "splenomegalic polycythæmia" or "erythræmia") is not greatly if at all concentrated. In other words, it proves that the polycythæmia cannot be accounted for by concentration of the blood as a whole. In our own case, indeed, the figures show that the blood plasma may have been very slightly concentrated,[19] probably as a result of capillary blood stasis. (It may be noted in this connexion that "clubbing" of the fingers and toes was not present in Bie and Maar's case, but was in our case.)

The albumin in the blood and blood serum has not, as far as we know, been estimated in cases of polycythæmia secondary to cardiac disease, but in cases of erythræmia Weintraud and Senator both found the percentage of albumin in the blood serum below the normal, and in an unpublished case of erythræmia G. Dorner estimated it at 7·38 to 7·55 per cent. (that is, below the normal, according to von Jaksch).

Anyhow, we have now decided evidence that the chronic polycythæmia of congenital heart disease is, like that of "erythræmia," associated with excess in the total blood-volume of the body ("plethora vera," "polyhæmia") and with excessive formation of red blood corpuscles in the bone marrow. This is doubtless also true of the polycythæmia sometimes associated with acquired heart disease. Thus Lorrain Smith and H. L. M'Kisack,[20] in the case of a boy, aged 12 years, suffering from adherent pericardium and chronic cyanosis, not only showed that the proportion of red cells to blood plasma was excessive (relative polycythæmia), but also demonstrated by the carbon-monoxide method that the total volume of blood was far beyond the normal standard, so that there was undoubtedly a condition of true plethora present. It is almost certain that in all chronic cardiac cases, whenever the erythrocyte count per cubic millimetre of blood is above the normal (relative polycythæmia), the total volume of blood in the whole body is

[19] The blood serum used in our case, as already mentioned, contained a little hæmoglobin.

[20] Lorrain Smith and M'Kisack: Transactions of the Pathological Society of London, 1902, vol. liii., p. 136.

likewise excessive. This is indeed what one would expect from the congested appearance in some patients of the face, lips, tongue, and retinæ (as seen by ophthalmoscopic examination) during life, and the hyperæmic condition of their viscera as seen at post-mortem examinations. It is also probable that the total blood volume may be excessive in many chronic cardiac cases even when a blood count shows absence of relative polycythæmia.

E. Weil[21] of Paris was the first to show that the secondary polycythæmia of heart disease is associated with an actual erythroblastic reaction in the bone marrow. In 1901, in post-mortem examinations on two children with congenital stenosis of the pulmonary orifice of the heart and chronic cyanosis, he found that there was red transformation of the bone marrow, microscopic sections of which showed that all traces of the normal fatty tissue had disappeared. His results have been confirmed by Mackey and others. In 1907 L G. J. Mackey[22] examined microscopic sections made by J. Miller from the bone marrow of a case similar to those of Weil, and obtained similar results to Weil. The polycythæmia of congenital heart disease and chronic cardiac insufficiency is therefore due to great erythroblastic activity of the bone marrow, and represents a true hyperplasia of the erythrocytes and of the erythrocyte-forming tissues of the body, which is, in fact, analogous to the myocardial hypertrophy found in conditions throwing abnormal work on the whole or a portion of the musculature of the heart.

Orthostatic albuminuria seems not to have been observed in most cases of congenital heart disease, but it was very marked in the present patient[23] and in a young man, aged 22 years, whose case was previously described by one of us.[24] We should expect to find it in other cases of congenital heart disease, if accompanied by chronic cyanosis and extreme polycythæmia, and in this connexion, as suggested to us by Dr. A. E. Garrod, the calcium content of the blood might be estimated in similar future cases.

[21] E. Weil: Comptes Rendus de la Société de Biologie, Paris, 1901, vol. liii., p. 713.

[22] L. G. J. Mackey: Birmingham Medical Review, 1907, vol. x., pp. 113, 177.

[23] The orthostatic albuminuria was apparently not a family peculiarity.

[24] F. P. Weber: A Case of Congenital Heart Disease, with Extreme Secondary Polycythæmia and Orthostatic Albuminuria, Edinburgh Medical Journal, 1909, New Series, vol. ii., p. 18

It is worth while drawing attention to the fact that the patient whose case we are now considering takes a good deal of open-air exercise, and, though it may tend temporarily to increase his cyanosis, he declares that he feels much better with exercise than without it. He thinks that an active industrious life suits him better than a lazy one.

The secondary polycythæmia in cases of congenital heart disease is seldom, if ever, rivalled in degree by the secondary polycythæmia which sometimes, as is well known, occurs in chronic acquired valvular affections (of the mitral valve) and in adherent pericardium. It is more nearly rivalled by the marked secondary polycythæmia occasionally associated with late stages of pulmonary emphysema, chronic bronchitis, asthma, old bilateral pleuritic adhesion, chronic interstitial pneumonia, and pulmonary fibrosis. The polycythæmia in all such cases differs from the polycythæmia (possibly of primary myelogenous origin) associated with chronic splenomegaly, which has been termed "erythræmia,"[25] by the not infrequent absence of real cyanosis in erythræmia, especially in its early stages.

What prognostic significance can be attached to the secondary polycythæmia in cardiac cases? In answer to this question we need only repeat what one of us has previously written. Just as hypertrophy of the walls of the heart is useful in so far as it compensates for mechanical defects in the valvular apparatus, so also is polycythæmia useful in so far as it compensates for difficulties in the proper oxygenation of the blood and tissues of the body; but just as in cardiac valvular disease great hypertrophy of the heart indicates some grave defect in the valvular mechanism, so also an extreme increase in the number of erythrocytes in the blood points to there being great impairment of the normal process of oxygenation of the body.

[25] Vide F. P. Weber, Quarterly Journal of Medicine, loc. cit.